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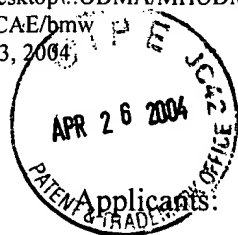


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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Barbara A. Gilchrest, Mina Yaar and Mark Eller

Application No.: 09/018,194 Group: 1647
Filed: February 4, 1998 Examiner: S. L. Wegert
Confirmation No.: 9447

For: Inhibition of Apoptosis in Keratinocytes by a Ligand of p75 Nerve Growth Factor Receptor (As Amended)

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INTERVIEW SUMMARY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

A telephonic interview was conducted on March 25, 2004. Participants were:

Examiner Sandra Wegert
Examiner Elizabeth Kemmerer
Inventor Barbara A. Gilchrest
Inventor Mina Yaar
Attorney Doreen M. Hogle
Attorney Carol A. Egner

The attorneys and inventors wish to thank the Examiners for holding the interview.

Arguments were presented that pertained to all the claims currently under examination.

No new exhibits or new Declarations were presented. Examiner Sandra Wegert was sent by fax

an informal paper, not to be entered, "Points to Consider for Telephonic Interview," preceding the interview.

No prior art was discussed, as the one remaining rejection is under 35 U.S.C. § 112, first paragraph.

Points Presented at Interview Relative to Enablement of the Claims

Keratinocytes either go into producing hair shaft or go into producing the stratum corneum. Keratinocytes in culture can be used to predict the behavior of keratinocytes in skin. The intracellular pathways the keratinocytes use to differentiate are the same. The apoptosis (cell death) pathways are the same for keratinocytes, whether they are in stratum corneum or in hair follicles. If the apoptotic pathway is blocked in keratinocytes, cell death is prevented, whether the keratinocytes are in stratum corneum or in hair follicles.

There are many factors affecting hair growth and those factors and their possible interactions are poorly understood. Despite the complexity, modulating one pathway can have an effect. Although the observed effect may not be absolute, and may not be a "cure" for hair loss, an observed effect on maintaining hair or slowing loss is nevertheless valued.

Male pattern baldness is not permanent hair loss. Rather, it is a phenomenon that results from a shift in the relative lengths of the phases of hair growth, anagen (growth), catagen (regression) and telogen (rest). In male pattern baldness, anagen is not long enough, resulting in only short, fine hairs. Therefore, an agent that changes the length of the phases of hair growth will have an effect on male pattern baldness.

Alopecia areata is real hair loss that occurs by an immunological mechanism. An infiltrate of T lymphocytes surrounds the keratinocytes, causing catagen.

UV irradiation of keratinocytes in cell culture is not meant to mimic, and does not mimic, the factors that contribute to male pattern baldness or to alopecia areata. Rather, UV is used only as an initiating event for apoptosis. In the model of hair loss using UV on cells in culture, the radiation is brief -- only long enough to activate pathways for the cells to commit suicide. The

p75 pathway is a common final pathway to cause apoptosis, found in all cells. UV is not the relevant stimulus that causes male pattern baldness, but sets in motion pathways going through the p75 receptor. The p75 receptor governs transitions of anagen through telogen. Applicants' method blocks the transition to catagen.

The experiments described in the Declaration of Barbara A. Gilchrest, M.D. Under 37 C.F.R. § 1.132, mailed to the United States Patent and Trademark Office on April 8, 2002, were reviewed. It was noted during the interview that experiments were performed on biopsies of mouse skin maintained in organ culture during the early stages of catagen. Cyclic peptide SEQ ID NO:9 (CATDIKGAEC) or diluent was added to the mouse organ explants as control. The cyclic peptide delayed catagen development of hair, showing that blocking neurotrophin receptor p75 activation is associated with delay of catagen initiation.

More recent experiments are consistent with these results. [See the attached abstract, labeled "Appendix," referred to by Dr. Gilchrest, but not presented at the time of the interview: Zhai S., Yaar M., Reenstra W., Gilchrest B.A. Elucidation of apoptotic pathways following activation of the 75 kDa neurotrophin receptor. *J. Invest. Dermatol.* 112:548, 1999 (Abstract 151).]

Examiner Wegert pointed out that the language in the claims -- Claim 33, for example -- is to maintaining hair growth, and suggested that what is observed from the experiment described in the Declaration is perhaps more accurately "delaying catagen" or "delaying hair loss." Applicants were invited to submit additional claims with alternative claim language.

Respectfully submitted,
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

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The Human Nude Phenotype: Congenital Alopecia and Severe T Associated with a Nonsense Mutation in the Wln Gene

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The nude mouse phenotype is characterized by congenital absence of hair, alopecia, and immunodeficiency. The nude mouse mutation is a mutation in the *u^hm* gene (winged-helix-forkhead winged helix transcription factor family member with restriction endonuclease III site) and skin. Identification of the human counterpart of the nude mutation is presumably because affected individuals succumb to the immunodeficiency and absence of hair can be appreciated. Recently, the simultaneous occurrence of severe immunodeficiency, congenital alopecia and nail dystrophy (MIM 264700) in a consanguineous Italian family was reported. One sibling marrow transplantation which corrected the immunodeficiency, but not the alopecia, suggested that this syndrome represented a candidate gene for the human *u^hm* gene. We found suggestive evidence of linkage to the human *u^hm* gene. We found suggestive evidence of linkage to human chromosome 17 ($\chi^2_{max} = 1.32$), identified a homozygous non-functional mutation in the *u^hm* gene in one of the affected individuals, and localized the expression of human *u^hm* to tissues involved in the hair cycle (epithelium), and in the hair and atheroma in the atherosclerotic arteries. The localization of the hair and atheroma in the

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Glucosaminoglycans Induce a Near-Total Suppression of Hyaluronan Synthesis in Fibroblasts and in Osteoblasts: A Molecular Mechanism Contributing to Wound Healing

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